JACC: CARDIOVASCULAR IMAGING VOL. 6, NO. 9, 2013

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2013.04.012

Libman-Sacks Endocarditis and Embolic Cerebrovascular Disease

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OBJECTIVES The aim of this study was to determine whether Libman-Sacks endocarditis is a pathogenic factor for cerebrovascular disease (CVD) in systemic lupus erythematosus (SLE).

BACKGROUND A cardioembolic pathogenesis of SLE CVD manifested as: 1) neuropsychiatric systemic lupus erythematosus (NPSLE), including stroke and transient ischemic attacks (TIA); 2) neurocognitive dysfunction; and 3) magnetic resonance imaging of focal brain lesions has not been established.

METHODS A 6-year study of 30 patients with acute NPSLE (27 women, 38 ± 12 years of age), 46 age- and sex-matched SLE controls without NPSLE (42 women, 36 ± 12 years of age), and 26 age- and sex-matched healthy controls (22 women, 34 ± 11 years of age) who underwent clinical and laboratory evaluations, transesophageal echocardiography, carotid duplex ultrasound, transcranial Doppler ultrasound, neurocognitive testing, and brain magnetic resonance imaging/magnetic resonance angiography. Patients with NPSLE were re-evaluated after 4.5 months of therapy. All patients were followed clinically for a median of 52 months.

RESULTS Libman-Sacks vegetations (87%), cerebromicroembolism (27% with 2.5 times more events per hour), neurocognitive dysfunction (60%), and cerebral infarcts (47%) were more common in NPSLE than in SLE (28%, 20%, 33%, and 0%) and healthy controls (8%, 0%, 4%, and 0%, respectively) (all $p \leq 0.009$). Patients with vegetations had 3 times more cerebromicroemboli per hour, lower cerebral blood flow, more strokes/TIA and overall NPSLE events, neurocognitive dysfunction, cerebral infarcts, and brain lesion load than those without (all $p \leq 0.01$). Libman-Sacks vegetations were independent risk factors of NPSLE (odds ratio [OR]: 13.4; $p < 0.001$), neurocognitive dysfunction (OR: 8.0; $p = 0.01$), brain lesions (OR: 5.6; $p = 0.004$), and all 3 outcomes combined (OR: 7.5; $p < 0.001$). Follow-up re-evaluations in 18 of 23 (78%) surviving patients with NPSLE demonstrated improvement of vegetations, microembolism, brain perfusion, neurocognitive dysfunction, and lesion load (all $p \leq 0.04$). Finally, patients with vegetations had reduced event-free survival time to stroke/TIA, cognitive disability, or death ($p = 0.007$).

CONCLUSIONS The presence of Libman-Sacks endocarditis in patients with SLE was associated with a higher risk for embolic CVD. This suggests that Libman-Sacks endocarditis may be a source of cerebral emboli. (J Am Coll Cardiol Img 2013;6:973–83) © 2013 by the American College of Cardiology Foundation

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Cerebrovascular disease (CVD) in systemic lupus erythematosus (SLE) is common, is associated with increased morbidity and mortality, and manifests as: 1) major neuropsychiatric systemic lupus erythematosus (NPSLE) syndromes of stroke, transient ischemic attacks (TIA), confusional state, or seizures; 2) acute or cumulative neurocognitive dysfunction; and 3) focal brain lesions on magnetic resonance imaging (MRI) (1–5). CVD in SLE is usually attributed to cerebritis, vasculitis, hypercoagulability, atherosclerosis, or antineuronal antibodies (5–9). However, CVD in SLE often occurs independently of these conditions (10–12). Libman-Sacks endocarditis characterized by noninfective inflammatory and/or thrombotic vegetations is also common in SLE and is associated with increased morbidity and mortality (13). The relationship of Libman-Sacks endocarditis with CVD in SLE has not been established because small, retrospective, or noncontrolled studies have used transthoracic echocardiography (TTE), a method with lower sensitivity and specificity than transesophageal echocardiography (TEE) for detection of Libman-Sacks endocarditis (14,15); because of incomplete clinical or imaging data not timed to clinical events; and because of inclusion of patients with confounding age-related heart and brain disease. Thus, this 6-year, fully integrated, controlled, cross-sectional, longitudinal study was designed to establish the relationship between Libman-Sacks endocarditis detected by TEE and cerebroembolism, NPSLE, neurocognitive dysfunction, and focal brain injury.

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ABBREVIATIONS AND ACRONYMS

CVD = cerebrovascular disease

MRA = magnetic resonance angiography

NPSLE = neuropsychiatric systemic lupus erythematosus

SLE = systemic lupus erythematosus

TEE = transesophageal echocardiography

TIA = transient ischemic attack

TTE = transthoracic echocardiography

METHODS

Study populations. The study design and protocol was approved by the National Institutes of Health and our institutional review board, and participants provided informed consent. From December 2006 to December 2012, 76 of 266 patients with SLE (29%) actively followed at the rheumatology clinics of the University of New Mexico were consecutively recruited and classified at enrollment into 2 study groups.

ACUTE NPSLE GROUP. Thirty patients (27 women, 38 ± 12 years of age) with NPSLE manifesting as acute stroke/TIA (n = 23), cognitive dysfunction (n = 11), confusional state (n = 7), or seizures (n = 4) were included in the acute NPSLE group. The occurrence of NPSLE in 30 of 266 screened patients over a 6-year period constituted cumulative and annual event rates of 11.3% and 1.9%, respectively, similar to those reported in inception studies (1).

SLE CONTROL GROUP. Forty-six age- and sex-matched patients with SLE (42 women, 36 ± 12 years of age) without clinically manifested acute or past NPSLE were included in the SLE control group.

Patients were excluded due to age <18 or >60 years, pregnancy, heart or brain disease unrelated to SLE, atrial fibrillation or flutter, cardiomyopathy, intracardiac thrombi, drug abuse, renal dysfunction, difficult venous access, self-withdrawal or noncompliance with study protocol, or contraindications to TEE or MRI.

For validation of blinded interpretation and diagnostic accuracy of tests and to provide a normality reference, 26 apparently healthy volunteers age- and sex-matched to patients were studied. Controls were recruited by the study coordinator from available listings of volunteers in the Office of Research of the Health Sciences Center, employees of the University of New Mexico, and patients' relatives or acquaintances. Candidate volunteers were then screened with a standard general health questionnaire.

All 102 participants underwent a standardized protocol of clinical and laboratory evaluations, TEE, carotid duplex ultrasound, transcranial Doppler ultrasound, complete neurocognitive testing, and brain MRI/magnetic resonance angiography (MRA) within 1 week of enrollment. All studies were coded, deidentified, and interpreted by experienced observers blinded to participants' clinical and imaging data.

Clinical and laboratory evaluations. Patients were characterized with regard to disease duration, activity, injury, therapy, and standard autoantibodies (11,16,17) (Online Table 1). All 102 participants

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This research was funded by grant RO1-HL04722-01-A6 from the National Institutes of Health/National Heart, Lung and Blood Institute and in part by grant 8UL1-TR000041 from the National Center for Research Resources. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 22, 2013; revised manuscript received April 18, 2013, accepted April 23, 2013.

were further characterized for demographics, atherogenic risk factors, and specific parameters of inflammation, platelet activity, coagulation, and fibrinolysis (Online Table 2).

Transesophageal echocardiography. Participants underwent complete TEE with IE-33 Philips systems (Philips Healthcare, Andover, Massachusetts) with images digitally acquired for offline interpretation. Heart valves were imaged in multiple planes at a depth of 4 to 8 cm with a narrow sector scan to improve image resolution.

CRITERIA FOR INTERPRETATION. *Libman-Sacks vegetations* were defined as abnormal localized echodensities with well-defined borders as either part of or adjacent to valve leaflets or subvalvular apparatus (13). Size of vegetations was determined by planimetry. *Valve thickening* was determined using M-mode imaging and was considered present when thickness >3 mm (mitral valve) or >2 mm (aortic valve) was observed in ≥2 leaflets or in 1 leaflet if associated with vegetation, at least mild regurgitation, or both (13,18). *Mitral or aortic regurgitation* assessed by standard color Doppler criteria was present if worse than mild or if mild and associated with a vegetation or thickening of the respective valve (13,19). In 30 randomly selected TEE studies (22 patients, 8 controls), interobserver agreement for detection of valve vegetations, thickening, and regurgitation were 93%, 83%, and 90%, respectively (kappa 0.87, 0.67, and 0.73, respectively).

The left atrium and ventricle were assessed for spontaneous echocardiographic contrast or thrombus; the atrial septum was interrogated by 2-dimensional, color Doppler, and saline contrast images for detection of aneurysms, patent foramen ovale, or atrial septal defects. The ascending aorta, arch, and descending thoracic aorta were assessed by 2-dimensional and M-mode images for intima-media thickening (≥2 SD above the mean of healthy controls) and plaques (focal thickening of intima-media exceeding 50% of the surrounding wall) (20).

Carotid duplex. From longitudinal B-mode images of both common carotid arteries, 6 measurements of intima-media thickness along the far and near walls were performed at end-diastole (21). Carotid intima-media thickening and plaques were determined with criteria described for the aorta.

Transcranial Doppler. Both middle cerebral arteries were interrogated for 90 min for detection of microemboli using a 2.0-MHz DWL Doppler Box with power Doppler M-mode, 32-gate spatial imaging, and dual-channel emboli detection software. Microemboli were defined as audible, high-intensity (>13 db), and <100 ms unidirectional signals within both Doppler blood flow velocity and vessel lumen (22). Intraobserver agreement for detection of microemboli was 96% (kappa 0.83).

Neurocognitive evaluation. Participants underwent complete neurocognitive testing for pre-morbid intelligence, attention, memory, language, processing speed, executive function, motor function, and global neurocognitive function (23).

Brain MRI/MRA. Standard T1-weighted, fluid-attenuated inversion recovery, and diffusion-weighted images were obtained. Dynamic susceptibility contrast MRI was performed in 89 participants (64 patients, 25 controls; 92%) to assess brain perfusion (24). Brain lesions were classified as old or recent cerebral infarcts and small focal periventricular or deep white abnormalities using standard criteria (3,4,10). Counts of brain lesions and hemispheric and whole-brain lesion load in cm^3 were determined using semiautomated methods (25). Cerebral atherosclerosis, thrombosis, vasculitis, or aneurysms were determined using MRA (26). Interobserver agreement for detection of brain lesions in 68 studies was 94% (kappa 0.88).

Follow-up. To further assess the relationship of Libman-Sacks vegetations with cerebroembolism and CVD, 18 of 23 surviving patients with NPSLE (78%) underwent re-evaluations after 4.5 months (interquartile range [IQR]: 2.1 to 8.4 months) of clinically indicated antimalarial (87%), corticosteroid (50%), immunosuppressive (58%), antiplatelet (71%), or anticoagulant (35%) therapy. Five patients had no follow-up studies because they were too ill to undergo TEE or MRI. All 76 patients underwent clinical follow-up for a median of 52 months (IQR: 24 to 64 months) for development of new or recurrent stroke/TIA, cognitive disability (defined as formal physician recommendation for cognitive disability and a global neurocognitive score ≥1.5 SD below pre-morbid intelligence score), or death.

Statistical analysis. Descriptive statistics are mean ± SD or median and IQR in asymmetrically distributed variables or frequencies (%). Comparisons among the 3 study groups (Table 1) were performed by analysis of variance for continuous measures and verified by Kruskal-Wallis tests. Two-tailed Fisher exact tests were used for binary measures. Pairwise comparisons among 3 groups for each variable were done by Fisher least significant differences method. Association of vegetations with cerebromicroembolism and neurological outcomes are reported in Table 2. The rate ratio (95% confidence interval [CI]) of microembolism in patients with NPSLE and SLE and in those with and without

Table 1. Findings on Cardiovascular and Brain Imaging and Neurocognitive Testing

	Acute NPSLE (n = 30)	SLE (n = 46)	Controls (n = 26)	p Value
Transesophageal echocardiography				
Valve vegetations	26 (87)*†	13 (28)	2 (8)	<0.001
Mitral valve	20 (67)*†	6 (13)	1 (4)	<0.001
Aortic valve	14 (47)*†	11 (24)	2 (8)	0.004
Valve thickening	26 (87)*†	16 (35)*	2 (8)	<0.001
Mitral valve	20 (67)*†	8 (17)*	0	<0.001
Aortic valve	18 (60)*†	12 (26)	2 (8)	0.002
Valve regurgitation	15 (50)*†	5 (11)	0	<0.001
Mitral valve	13 (43)*†	4 (9)	0/25	<0.001
Aortic valve	2 (7)	3 (7)	0	0.60
Any valve abnormality	28 (93)*†	18 (39)*	3 (12)	<0.001
PFO or interatrial septal aneurysm	1 (3)†	11 (24)	2 (8)	0.03
LV ejection fraction <50%	2 (7)	0	0	0.15
Aorta intima-media thickness	0.88 ± 0.37*	0.80 ± 0.23*	0.66 ± 0.15	0.01
Aorta intima-media thickening	7/29 (24)	10/45 (22)	1 (4)	0.07
Aorta plaque (any portion)	9 (30)*	8 (17)*	0	0.007
Aorta intima-media thickening or plaque	11 (37)*	14 (30)*	1 (4)	0.006
Carotid artery duplex				
Intima-media thickness	0.55 ± 0.11*†	0.50 ± 0.07	0.48 ± 0.08	0.01
Intima-media thickening	4 (13)	1 (2.2)	1 (4)	0.11
Plaque	5 (17)	1 (2.2)	2 (8)	0.06
Intima-media thickening or plaque	8 (27)†	2 (4)	3 (12)	0.02
Transcranial Doppler				
Right or left MCA microemboli	8 (27)*† 17 events/43.1 h*†	9 (20) 11 events/68.5 h*	0	0.009; HR: 2.5 (p = 0.02)
Neurocognitive z-scores				
Clinical domain				
Pre-morbid intelligence	−0.67 ± 1.17 (27)	−0.46 ± 0.93 (45)	−0.06 ± 1.03	0.10
Attention	−3.14 ± 3.60*†	−0.91 ± 0.92 (45)	−0.06 ± 0.82	<0.001‡
Memory	−1.54 ± 1.43 (29)*	−1.03 ± 0.90 (45)*	−0.056 ± 0.81	<0.001‡
Language	−1.02 ± 1.04 (27)*	−0.99 ± 1.16 (45)*	−0.05 ± 0.89	<0.001‡
Processing speed	−2.19 ± 1.95 (28)*†	−0.87 ± 1.15 (45)*	−0.06 ± 0.93	<0.001‡
Executive function	−3.58 ± 3.58 (29)*†	−1.63 ± 2.20 (45)*†	−0.10 ± 0.79	<0.001‡
Motor function	−5.17 ± 8.67 (26)*†	−1.70 ± 1.66 (37)	−0.056 ± 0.63	<0.00‡
Global	−2.76 ± 2.54*†	−1.19 ± 0.91 (45)*†	−0.07 ± 0.52	<0.001‡
Global abnormal§	18 (60)*†	15 (33)*	1 (4)	<0.001‡
Brain lesions on MRI				
Any focal brain lesion	22 (73)*†	19/45 (42)*‖	4 (15)‖	<0.001
Focal brain lesions, n	12 (3, 47)*	2 (0, 9)	0 (0, 2)	<0.001¶
Old or recent cerebral infarcts	14 (47)*†	0	0	<0.001
Cerebral infarcts, n	0 (0, 2)*†	0	0	<0.001¶
White matter abnormalities	20 (67)*†	18/45 (40)*	4 (15)	<0.001
White matter abnormalities, n	9 (1, 46)*†	2 (0, 9)	0 (0, 2)	<0.001¶
White matter brain lesion load, cm^3				
Left hemisphere	0.96 (0.16, 2.21)*†	0.13 (0.05, 0.23)	0.04 (0.03, 0.15)	0.003¶
Right hemisphere	1.23 (0.18, 2.84)*	0.11 (0.05, 0.24)	0.05 (0.03, 0.10)	0.01¶
Whole brain	2.92 (3.18, 5.55)*†	0.26 (0.13, 0.38)	0.13 (0.07, 0.23)	0.002¶

Values are n (%), mean ± SD (range), or median (IQR). *p < 0.05 compared with controls by Fisher post hoc least significant differences method. †p < 0.05 for acute neuropsychiatric systemic lupus erythematosus (NPSLE) compared with SLE by Fisher post hoc least significant differences method. ‡All p ≤ 0.009 after simultaneously adjusting for education, pre-morbid intelligence, and depression index. §Global abnormal defined as ≥1.5 standard deviations (SD) below the mean total of controls. ‖One SLE patient did not complete magnetic resonance imaging (MRI) studies due to claustrophobia; includes 2 controls with history of sports-related head trauma. ¶By Kruskal-Wallis test.

HR = hazard ratio; IQR = interquartile range; LV = left ventricle; MCA = middle cerebral artery; PFO = patent foramen ovale.

vegetations was estimated by Poisson regression with individual observation time as the offset. Neurocognitive z-scores were computed using controls as reference. Differences in cerebral blood flow in gray and white matter of 4 cerebral lobes and 2 hemispheres due to vegetations and microembolism were analyzed by repeated-measures analysis of variance. Using clinical, laboratory, and cardiovascular imaging measures listed in Table 1 and Online Tables 1 and 2, significant risk factors in univariate logistic regression for NPSLE, neurocognitive dysfunction, brain lesions, and all 3 outcomes combined were considered candidate risk factors in multivariate logistic regression analyses (Table 3). The list of candidate risk factors is detailed in Online Table 3. Effects are reported as adjusted odds ratios (ORs) and 95% CI with Firth bias correction in near-separation conditions. The effect of therapy in follow-up was assessed by Wilcoxon signed-rank test as a robust, nonparametric paired comparison (Table 4). Kaplan-Meier event-free survival curves for stroke/TIA, cognitive disability, or death related to vegetations were compared by log-rank tests. A Cox proportional hazards model was used to select predictors of this combined event. Two-tailed p values ≤0.05 were considered significant. All statistical analyses were performed in SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Clinical characteristics. Patients with NPSLE as compared with SLE were more often treated with statins and aspirin or warfarin, were more commonly positive for SSA and β2-glycoprotein antibodies, had higher triglyceride levels, had lower hemoglobin and serum albumin levels, and had higher levels of D-dimer and tissue plasminogen antigen (all p ≤ 0.04) (Online Tables 1 and 2). Patients with NPSLE and SLE differed from controls in multiple clinical and laboratory parameters.

Findings on cardiovascular imaging, neurocognitive testing, and brain MRI. Patients with NPSLE as compared with SLE and healthy controls had more Libman-Sacks vegetations, valve thickening, valve regurgitation, any valve abnormality, mild carotid atherosclerosis, cerebral microembolism (Poisson regression, 2.5 times more events per hour; 95% CI: 1.2 to 5.3; p = 0.02), neurocognitive dysfunction, and brain lesions and lesion load (all p ≤ 0.02) (Table 1). Patent foramen ovale and interatrial septal aneurysms were more common in patients with SLE than in patients with NPSLE (p = 0.03).

Vegetations were of oval shape, heterogeneous or soft tissue echoreflectance, sessile, and of variable maximal diameter (5.8 ± 2.7 mm; range 2.8 to 14 mm) and area (0.37 ± 0.36 cm^2; range 0.04 to 1.51 cm^2); were seen on the atrial side and tips of mitral leaflets and on the ventricular or aortic side of aortic cusps; and were highly associated with valve thickening (81% to 92%; p < 0.001) (Online Videos 1, 1A, 2A, 2B, 2E, 2F, 3A, 3D, 3F, 4A, 5A, 5D, 5E, and 5F).

Cerebromicroembolism was similarly frequent in the right and left middle cerebral arteries. Consequently, focal brain lesions always involved both hemispheres (Fig. 1, Online Figs. 1 to 5).

Table 2. Association of Libman-Sacks Vegetations With Microembolism, Acute Stroke/TIA and Overall NPSLE, Neurocognitive Dysfunction, and Brain Lesions and Lesion Load

	Patients With Vegetations (n = 39)	Patients Without Vegetations (n = 37)	p Value
Microembolism			
Right or left MCA microemboli	12 (31) 21 events/56.6 h	5 (14) 7 events/55 h	Adjusted HR*: 3.0; p = 0.01
NPSLE			
Acute stroke/TIA	22 (56)	1 (3)	<0.001
Acute overall NPSLE	26 (67)	4 (11)	<0.001
Neurocognitive z-scores			
Attention	−2.36 ± 3.00	−0.82 ± 0.91	0.02†
Memory	−1.75 ± 1.27	−0.79 ± 1.00	0.001†
Processing speed	−1.90 ± 1.92	−0.90 ± 1.15	0.04†
Executive function	−3.31 ± 3.60	−1.68 ± 2.53	0.03†
Motor function	−4.38 ± 7.40	−1.40 ± 1.54	0.005†
Global	−2.42 ± 2.32	−1.17 ± 0.98	0.01‡
Focal brain lesions			
Focal brain lesions	28 (72)	12/36 (34)§	<0.001
Focal brain lesions, n	9 (3, 39)	1 (0, 8)	0.004†
Cerebral infarcts	14 (36)	0/36	<0.001
Cerebral infarcts, n	0 (0, 2)	0	<0.001†
White matter lesions	25/37 (68)	12/36 (34)	0.005
White matter lesions, n	8 (1, 37)	1 (0, 8)	0.004†
Brain lesion load, cm^3			
Left hemisphere	0.05 (0, 1.23)	0 (0, 0.09)	0.016†
Right hemisphere	0.14 (0, 1.15)	0.01 (0, 0.06)	0.002†
Whole brain	0.18 (0, 2.34)	0.026 (0, 0.16)	0.008†

Values are n (%), mean ± SD, or median (IQR). *Poisson regression with repeated measures adjusting for PFO, interatrial septal aneurysm, carotid or aortic atherosclerosis, and antiphospholipid antibodies. †Wilcoxon test. ‡p = 0.02 after simultaneously adjusting for age, depression index, pre-morbid intelligence, and education. §One of the patients without vegetations had no MRI due to claustrophobia.
TIA = transient ischemic attack; other abbreviations as in Table 1.

Table 3. Independent Risk Factors of Acute NPSLE, Neurocognitive Dysfunction, Brain Lesions on MRI, and All 3 Outcomes Combined

	Odds Ratios (95% CI)	p Value*
Acute NPSLE		
Valve vegetations	13.40 (3.31–54.35)	<0.001
Valve regurgitation	5.10 (1.19–21.93)	0.03
Triglyceride levels (per 20 mg/dl)	1.27 (1.04–1.53)	0.02
Global neurocognitive dysfunction		
Vegetations and microembolism	8.01 (1.51–42.62)	0.01
Smoking (currently)	3.79 (1.16–12.40)	0.03
Non-neurological SLICC damage index	1.50 (1.06–2.13)	0.02
Age at diagnosis of SLE (per 10 years)	2.08 (1.27–3.40)	0.004
Focal brain lesions		
Valve vegetations	5.57 (1.72–18.01)	0.004
P-selectin	1.04 (1.00–1.07)	0.02
Complement C4	1.12 (1.03–1.22)	0.009
Acute NPSLE, cognitive dysfunction, or brain lesions		
Valve vegetations	7.49 (2.49–22.5)	<0.001†
Triglyceride levels (per 20 mg/dl)	1.28 (1.03–1.60)	0.03
P-selectin	1.05 (1.01–1.09)	0.02
Complement C4	1.17 (1.04–1.32)	0.008

*p values for multivariate analysis adjusted for other variables in the "best" stepwise model. †OR and p value adjusted in "best" stepwise model of predictors selected from all 3 components/outcomes as listed above.
SLICC = Systemic Lupus International Collaborative Clinics; other abbreviations as in Table 1.

Association of Libman-Sacks vegetations with cerebromicroembolism and CVD. As noted in Table 1, patients without NPSLE (SLE group) commonly had vegetations (28%), cerebromicroemboli (20%), cognitive dysfunction (33%), and brain lesions (42%), suggestive of subclinical cerebroembolism. Therefore, for better definition of the association of vegetations with cerebromicroembolism, NPSLE, cognitive dysfunction, and brain injury, all patients with SLE were stratified into those with and without vegetations. As shown in Table 2, 39 patients with vegetations compared with 37 without vegetations had 3 times more cerebromicroembolic events per hour after simultaneously adjusting for patent foramen ovale, interatrial septal aneurysm, carotid or aortic atherosclerosis, and antiphospholipid antibodies (95% CI: 1.3 to 7.2; $p = 0.01$), more stroke/TIA and overall NPSLE events, lower neurocognitive scores, and more brain lesions and lesion load (all $p \leq 0.04$). Also, 12 patients with vegetations and microemboli as compared with 32 patients with neither had lower cerebral blood flow (Fig. 2), more stroke/TIA and NPSLE events, lower neurocognitive scores, and more cerebral infarcts and lesion load (all $p \leq 0.03$) (Online Table 4).

Independent risk factors for CVD. Libman-Sacks vegetations (OR: 13.4; $p < 0.001$), valve regurgitation, and triglyceride levels were independent risk factors for NPSLE; vegetations and cerebromicroemboli (OR: 8.0; $p = 0.01$), current smoking, non-neurological damage index, and age at diagnosis of SLE were risk factors for neurocognitive dysfunction; vegetations (OR: 5.6; $p = 0.004$) and P-selectin and complement C4 levels were risk factors for focal brain lesions; and vegetations (OR: 7.5; $p < 0.001$), triglyceride levels, and P-selectin and C4 levels were risk factors for all 3 outcomes combined (Table 3).

Follow-up findings. In support of the relationship of Libman-Sacks vegetations with cerebroembolism and CVD, re-evaluations in 18 of 23 survivors (78%) of treated NPSLE demonstrated improvement of vegetations, cerebromicroembolism, cerebral blood flow, neurocognitive function, and brain lesion load (all $p \leq 0.04$) (Table 4, Online Figs. 1 to 5). During follow-up, 19 of 76 patients (25%) developed major clinical events. Twelve patients (16%) developed new or recurrent stroke/TIA (9 of 12 patients underwent re-evaluations, and all had recurrent or persistent vegetations [n = 8], cerebromicroemboli [n = 5], or brain lesions [n = 9]) (Online Figs. 1 to 5), 10 (14%) developed cognitive disability, and 7 (9%) died. Fifteen of 39 patients with vegetations (38%) developed events as compared with 4 of 37 without vegetations (11%; $p = 0.008$). Kaplan-Meier analysis demonstrated reduced event-free survival in patients with vegetations (time to death $p = 0.06$; time to disability $p = 0.04$; time to stroke/TIA $p = 0.003$; time to combined event $p = 0.007$) (Fig. 3). Vegetations, aortic or carotid atherosclerosis, and P-selectin levels were independent predictors of the combined event by Cox proportional hazards stepwise analysis (hazard ratio: 4.8, 4.1, and 1.4, respectively; all $p \leq 0.008$).

DISCUSSION

This 6-year, fully integrated, controlled, cross-sectional, longitudinal study revealed 5 major findings: 1) patients with NPSLE as compared with SLE had more Libman-Sacks vegetations, cerebromicroemboli, neurocognitive dysfunction, and focal brain lesions; 2) patients with vegetations had 3.0 times more cerebromicroemboli per hour, lower cerebral perfusion, more stroke/TIA and overall

NPSLE events, greater neurocognitive dysfunction, and greater brain injury; 3) valve vegetations were strong independent risk factors for stroke/TIA and NPSLE, neurocognitive dysfunction, brain lesions, and all 3 outcomes combined; 4) vegetations, cerebromicroembolism, NPSLE, neurocognitive dysfunction, and brain perfusion and lesion load improved with anti-inflammatory and/or antithrombotic therapy; and 5) patients with vegetations had poor outcomes, with reduced event-free time to stroke/TIA, cognitive disability, or death. These findings support that Libman-Sacks vegetations may generate platelet or fibrin macroemboli or microemboli that occlude cerebral vessels and result in reduced cerebral perfusion, ischemic brain injury, stroke/TIA, nonfocal NPSLE syndromes, neurocognitive dysfunction or disability and contribute to death. Thus, Libman-Sacks endocarditis may be a common and under-recognized pathogenesis of embolic CVD in SLE.

Age at diagnosis of SLE, non-neurological damage index, triglyceride levels, smoking, P-selectin (a cell adhesion molecule indicative of platelet activation and aggregation and endothelial cell activation or injury) levels (27), and complement C4 levels were also independent risk factors of CVD. Thus, disease duration and severity, atherogenic risk factors, platelet aggregation, and endothelial inflammation may be risk factors for valve vegetations, endothelial dysfunction, early atherosclerosis, and thrombosis and thus either contribute to thromboembolic CVD or are independent risk factors for CVD (28).

Previous, often retrospective, noncontrolled, or nonintegrated clinical and pathological studies support our findings. In a TTE study of 105 patients, unspecified valve disease was detected in 7 of 18 patients (39%) with past stroke (29). In our 1996 controlled study of 69 patients undergoing serial TEE, Libman-Sacks endocarditis detected in 61% of patients was associated with 11% incidence of stroke/TIA and a mortality of 12% during a 5-year follow-up (13). In another TTE study, any valve abnormality detected in 44% of 71 patients was associated with past stroke/TIA (30). In 3 retrospective studies from our institution (2 using TEE), valve vegetations were associated with past stroke/TIA, nonfocal NPSLE, and brain lesions on MRI (31–33). In a prospective noncontrolled TTE study, Libman-Sacks vegetations detected in 11% of 342 patients with SLE were associated with a higher incidence of stroke/TIA (14.8% in those with vs. 3% in those without vegetations) during a 4-year follow-up (34). With transcranial Doppler in 70 patients, 39% of 38 patients with versus none of 32 without antiphospholipid antibodies had microembolism associated with cerebrovascular ischemia and mitral valve prolapse (35). In another study (n = 53), patients with versus those without NPSLE had 5.4 ± 1.1 versus 0.3 ± 0.8 microemboli per hour, respectively (36). Microembolism in 9% of 55 patients in one study and in 15% of 109 patients in another study was associated with cerebral infarcts and/or cognitive dysfunction (37,38). Microembolism in 10.3% of 68 patients was more common in those with than without NPSLE (25% vs. 2.2%, respectively) (39). In these transcranial Doppler studies, valve disease was not assessed, but cerebromicroembolism was not associated with atherogenic risk factors or carotid atherosclerosis and was associated with antiphospholipid antibodies only in one study. In a post-mortem study of 50 patients, 9 of 10 patients with cerebral infarcts had

Table 4. Findings on Initial and Follow-up Cardiovascular and Brain Imaging and Neurocognitive Testing in 18 Patients With Treated NPSLE

Finding	Initial Study	Follow-up Study	p Value*
Transesophageal echocardiography			
Vegetations, n	2.0 ± 1.41	1.33 ± 1.28	0.03
Vegetations, area, cm^2	0.38 ± 0.46	0.18 ± 0.19	0.09
Transcranial Doppler			
Right or left MCA microemboli	5 patients (28%) with 14 microemboli	0	0.007†
Neurocognitive z-scores			
Attention	−3.55 ± 4.24	−2.26 ± 3.20	0.002
Memory	−1.62 ± 1.64	−0.88 ± 1.61	0.001
Motor function	−6.43 ± 10.46	−2.32 ± 2.70	0.002
Processing speed	−2.17 ± 2.01	−1.73 ± 2.41	0.02
Global cognitive dysfunction	−3.12 ± 3.08	−1.86 ± 2.32	<0.001
Brain perfusion, ml/min/100 g of tissue, (n = 11)			Δ%/p value*
Overall gray matter	28.10 ± 18.04	33.87 ± 15.02	34%/0.02
Overall white matter	14.36 ± 9.73	17.47 ± 6.88	38%/0.02
Frontal lobe (gray matter)	26.45 ± 17.58	32.19 ± 14.62	36%/0.02
Frontal lobe (white matter)	12.76 ± 9.14	15.60 ± 6.53	40%/0.01
Parietal lobe (gray matter)	29.25 ± 19.16	35.78 ± 15.20	38%/0.02
Parietal lobe (white matter)	13.87 ± 9.02	17.21 ± 6.19	41%/0.02
Temporal lobe (gray matter)	28.23 ± 16.97	33.78 ± 15.21	31%/0.04
Temporal lobe (white matter)	14.70 ± 10.31	17.85 ± 7.68	38%/0.02
Occipital lobe (gray matter)	28.46 ± 18.62	33.73 ± 15.39	32%/0.03
Occipital lobe (white matter)	16.10 ± 10.56	19.21 ± 7.27	35%/0.02
Brain lesion load			
Whole brain lesion load, cm^3	0.68 (0.17, 3.93)	0.55 (0.07, 1.74)	0.03

Values are mean ± SD, n (%), or median (IQR). *Wilcoxon signed-rank test. †Poisson regression with repeated measures.
Abbreviations as in Table 1.

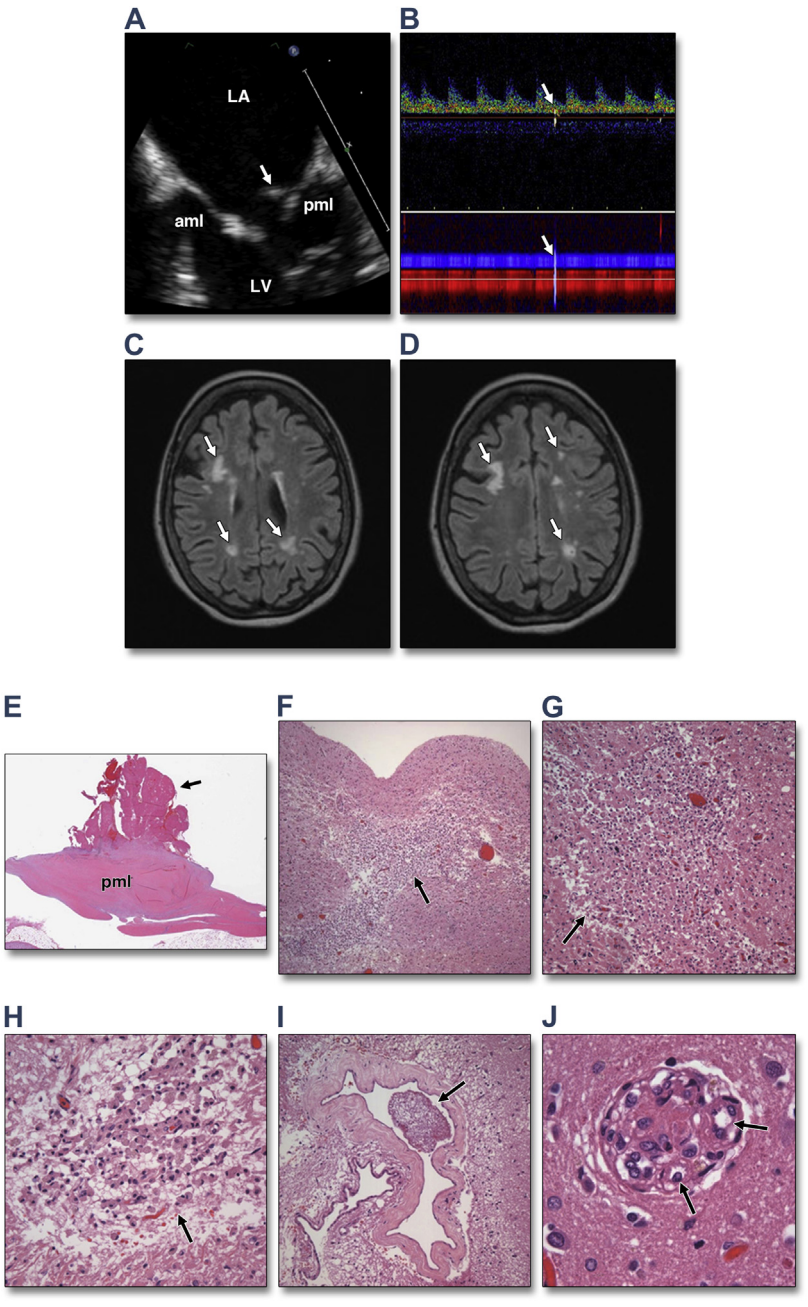

Figure 1. 55-Year-Old Woman With SLE and Acute Transient Ischemic Attack

(A) This transesophageal echocardiography view demonstrates a moderately sized, elongated, sessile, and heterogeneously echoreflectant Libman-Sacks vegetation **(arrow)** on the atrial side of the posterior mitral leaflet (pml) (Online Video 1). Moderate thickening and sclerosis with decreased mobility of the mid and distal portions of the anterior mitral leaflet (aml) and pml are noted. **(B)** Transcranial Doppler ultrasound demonstrates a microembolic signal on the spectral Doppler **(upper arrow)** and vessels lumen **(lower arrow)** traveling through the left middle cerebral artery (red power M-mode) and anterior communicating artery (blue power M-mode). **(C and D)** Brain magnetic resonance imaging demonstrates multiple, bilateral, and variably sized periventricular and deep white matter infarcts **(arrows)**. This patient had 75 brain lesions and a lesion load of 6.04 cm^3. Her global neurocognitive z-score was −4.28, indicative of severe neurocognitive dysfunction. **(E)** Histopathology with hematoxylin and eosin (H&E 40×) stains demonstrates thickening and fibrosis of the posterior leaflet with a well-adhered, verrucoid, fibrinous vegetation **(arrow)**. **(F)** (H&E 20×) Subacute cerebral infarct at the junction of the white and gray matter with necrotic debris and moderate cellular infiltration **(arrow)**. **(G and H)** (H&E 40× and 100×, respectively) Old deeper (white matter) infarct with liquefactive necrosis, residual macrophages, and gliosis **(arrows)**. **(I)** (H&E 100×) Large cerebral vessel with fibrin thrombi **(arrow)**. **(J)** (H&E 100×) Small cerebral vessel with fibrin thrombi and neoangiogenesis **(arrows)**. Multiple subacute and old microinfarcts and fibrin thrombosed microvasculature with neoangiogenesis characteristic of chronic cardiothromboembolic disease were demonstrated in both cerebral hemispheres. Please also see Online Videos 1A, 2A, 2B, 2E, 2F, 3A, 3D, 3F, 4A, 5A, 5D, 5E, and 5F. LA = left atrium; LV = left ventricle; SLE = systemic lupus erythematosus.

Libman-Sacks endocarditis, chronic valvulitis, or left heart thrombus (40). In 57 fatal NPSLE cases, 50% had multiple cerebral infarcts with fibrin or platelet thromboemboli (41). In a study of 14 patients, focal white matter lesions and cerebral infarcts on pre-mortem MRI correlated highly with old and acute cerebral infarcts and microthromboemboli on histopathology (10). Eight of these 14 patients (57%) had Libman-Sacks endocarditis. In these pathological studies, vasculitis, cerebritis, and atherosclerosis were rare. In contrast to prior studies, the present study is the largest and first fully integrated study linking Libman-Sacks vegetations with cerebromicroembolism, cerebral hypoperfusion, ischemic brain injury, stroke/TIA, overall NPSLE, neurocognitive dysfunction, and death. Improvement with current therapy of Libman-Sacks vegetations, cerebromicroembolism, brain perfusion and injury, and neurocognitive dysfunction further support a causal association of Libman-Sacks endocarditis and CVD.

The present study has potential limitations. The difficulty of testing patients at onset of CVD and before therapy; transcranial Doppler sampling for only 90 min; and exclusion of patients with renal dysfunction, and thus more aggressive disease, may have reduced the strength of the association of vegetations with cerebromicroembolism and CVD. The study in a tertiary care center may have overestimated the association of vegetations with CVD. However, patients were selected for acute CVD and not for valve vegetations; thus, a true association between vegetations and CVD is likely. A hypothetical study design in which "exposure" (vegetations) precedes the "outcome" (CVD) may be limited in determining causality due to common resolution of valve vegetations over time (13) and multiplicity of potential pathogenesis of CVD. Therefore, such a design would require re-evaluations during acute CVD, as in our study design. Cerebroembolism from Libman-Sacks vegetations leading to breakdown of the blood-brain barrier may be an important route of entry of antineuronal antibodies into the brain and should be investigated in future studies. Detection of focal nodularities or vegetation-like abnormalities in 2 apparently healthy controls was confirmed by a second independent observer, and it is known that apparently healthy populations may have a 9% to 15% prevalence of silent valve disease (13,14,42). However, we cannot exclude that such vegetation-like structures may have been mistaken with normal variant mimickers of valve masses such as atypical lamellar type of Lambl excrescences or less likely nodes of Aranti.

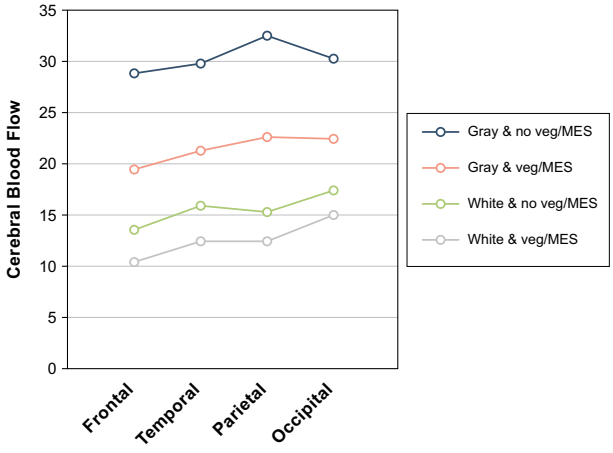

Figure 2. Cerebral Blood Flow in Patients With SLE With Vegetations and Cerebromicroembolism

Cerebral blood flow (ml/min/100 g of tissue) in the gray and white matter is significantly lower in 11 patients with vegetations and cerebromicroemboli as compared with that in 24 patients with neither across the 4 cerebral lobes and left and right hemispheres (repeated-measures analysis of variance $p \leq 0.001$ for both gray and white matter). Gray & no veg/MES = gray matter perfusion in patients with no vegetations and no cerebromicroembolism; gray & veg/MES = gray matter perfusion in patients with vegetations and cerebromicroembolism; white & no veg/MES = white matter perfusion in patients with no vegetations and no cerebromicroembolism; white & veg/MES = white matter perfusion in patients with vegetations and cerebromicroembolism; other abbreviations as in Figure 1.

This study has several clinical implications. Libman-Sacks endocarditis is a strong independent risk factor for CVD in SLE. An increased awareness of this association should lead to a greater focus

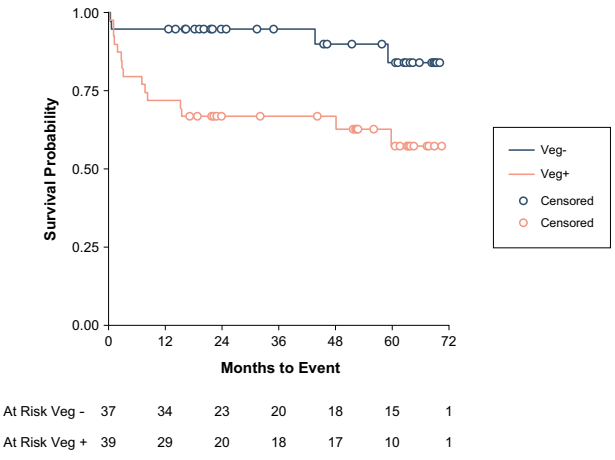

Figure 3. Kaplan-Meier Event-Free Survival in Patients With SLE With and Without Vegetations

During follow-up, the event-free survival from stroke/transient ischemic attack, cognitive disability, or death of patients with vegetations (Veg+) was significantly lower than in those without vegetations (Veg−) ($p = 0.007$). Abbreviations as in Figure 1.

on the cardiovascular evaluation of patients with SLE and CVD including use of TEE for increased detection of vegetations. Because of the semi-invasive nature of TEE, patients with SLE should be carefully selected for undergoing such a procedure with the highest diagnostic yield. Our study results support that it is appropriate to perform TEE in patients with SLE with: 1) acute, recent (within 2 to 4 weeks), or recurrent stroke or TIA; or 2) acute, recent (within 2 to 4 weeks), or recurrent nonfocal neurological manifestations of confusional state, cognitive dysfunction, or seizures, if they also have focal brain abnormalities on MRI or cerebromicroembolism on transcranial Doppler. Clinical findings integrated with those of TEE, transcranial Doppler, and brain MRI should lead to a prompt and accurate diagnosis and treatment of Libman-Sacks endocarditis and CVD, which may prevent recurrence or progression of CVD.

CONCLUSIONS

The identification of valve disease in SLE as a potential source of embolism resulting in ischemic CVD may also apply to other conditions commonly associated with valve and brain disease such as rheumatoid arthritis, primary antiphospholipid syndrome, rheumatic fever, and Behcet disease (42–46). Current nonstandardized pharmacotherapy seems beneficial for Libman-Sacks endocarditis and CVD. However, there is a need for a randomized controlled study to determine the most appropriate pharmacotherapy (antiplatelet, anticoagulation, immunosuppressive, neuroprotective, lipid-lowering, or combined therapy) for primary and secondary prevention of potentially disabling and life-threatening Libman-Sacks endocarditis and CVD.

Acknowledgments

The authors give special thanks to Dr. Warren Laskey for his insightful review of the manuscript and to Janeen Sharrar, RN, and Julia Middendorf, RN, for their outstanding job in the coordination of this study.

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REFERENCES

1. Hanly JG, Urowitz MB, Su L, et al. Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. Ann Rheum Dis 2010;69:529–35.
2. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus erythematosus. Arthritis Rheum 1999; 42:599–608.
3. Luyendijk J, Steens SC, Ouwendijk WJ, et al. Neuropsychiatric systemic lupus erythematosus: lessons learned from magnetic resonance imaging. Arthritis Rheum 2011;63:722–32.
4. Sibbitt WL Jr., Schmidt PJ, Hart BL, Brooks WM. Fluid attenuated inversion recovery (FLAIR) imaging in neuropsychiatric systemic lupus erythematosus. J Rheumatol 2003;30: 1983–9.
5. Bernatsky S, Clarke A, Gladman DD, et al. Mortality related to cerebrovascular disease in systemic lupus erythematosus. Lupus 2006;15:835–9.
6. Efthimiou P, Blanco M. Pathogenesis of neuropsychiatric systemic lupus erythematosus and potential biomarkers. Mod Rheumatol 2009;19:457–68.
7. Syuto T, Shimizu A, Takeuchi Y, et al. Association of antiphosphatidylserine/prothrombin antibodies with neuropsychiatric systemic lupus erythematosus. Clin Rheumatol 2009;28:841–5.
8. Govoni M, Bombardieri S, Bortoluzzi A, et al. Factors and comorbidities associated with first neuropsychiatric event in systemic lupus erythematosus: does a risk profile exist? A large multicentre retrospective cross-sectional study on 959 Italian patients. Rheumatology (Oxford) 2012;51:157–68.
9. Gono T, Kawaguchi Y, Kaneko H, et al. Anti-NR2A antibody as a predictor for neuropsychiatric systemic lupus erythematosus. Rheumatology (Oxford) 2011;50:1578–85.
10. Sibbitt WL Jr., Brooks WM, Kornfeld M, Hart BL, Bankhursts AD, Roldan CA. Magnetic resonance imaging and brain histopathology in neuropsychiatric systemic lupus erythematosus. Semin Arthritis Rheum 2010;40:32–52.
11. Brey RL, Muscal E, Chapman J. Antiphospholipid antibodies and the brain: a consensus report. Lupus 2011; 20:153–7.
12. Kozora E, West SG, Maier SF, et al. Antibodies against N-methyl-D-aspartate receptors in patients with systemic lupus erythematosus without major neuropsychiatric syndromes. J Neurol Sci 2010;295:87–91.
13. Roldan CA, Shively BK, Crawford MH. An echocardiographic study of valvular heart disease associated with systemic lupus erythematosus. N Engl J Med 1996;335:1424–30.
14. Roldan CA, Qualls CR, Sopko KS, Sibbitt WL Jr. Transthoracic versus transesophageal echocardiography for detection of Libman-Sacks endocarditis: a randomized controlled study. J Rheumatol 2008;35:224–9.
15. Omdal R, Lunde P, Rasmussen K, Mellgren SI, Husby G. Transesophageal and transthoracic echocardiography and Doppler-examinations in systemic lupus erythematosus. Scand J Rheumatol 2001;30:275–81.
16. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH; Committee on Prognosis Studies in SLE. Derivation of the SLEDAI. A disease activity index for lupus patients. Arthritis Rheum 1992;35:630–40.
17. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American

College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.
18. Crawford MH, Roldan CA. Quantitative assessment of valve thickness in normal subjects by transesophageal echocardiography. Am J Cardiol 2001; 87:1419–23.
19. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
20. Roldan CA, Joson J, Sharrar J, Qualls CR, Sibbitt WL Jr. Premature aortic atherosclerosis in systemic lupus erythematosus: a controlled transesophageal echocardiographic study. J Rheumatol 2010;37:71–8.
21. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society of Vascular Medicine and Biology. J Am Soc Echocardiogr 2006;19:943–54.
22. Choi Y, Saqqur M, Asil T, et al. A combined power M-mode and single gate transcranial Doppler ultrasound microemboli signal criteria for improving emboli detection and reliability. J Neuroimaging 2009;32:1–9.
23. Kozora E, Ellison MC, West S. Reliability and validity of the proposed American College of Rheumatology neuropsychological battery for systemic lupus erythematosus. Arthritis Rheum 2004;51:810–8.
24. Gasparovic CM, Roldan CA, Sibbitt WL Jr., et al. Elevated cerebral blood flow and volume in systemic lupus measured by dynamic susceptibility contrast magnetic resonance imaging. J Rheumatol 2010;37:1834–43.
25. Scully M, Anderson B, Lane T, et al. An automated method for segmenting white matter lesions in lupus through multilevel morphometric feature classification. Front Hum Neurosci 2010;4:1–7.
26. Feldman E, Wilterdink JL, Kosinski A, et al. Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) Trial. Neurology 2007;68: 2099–106.
27. Rouzet F, Bachelet-Violette L, Alsac JM, et al. Radiolabeled fucoidan as a P-selectin targeting agent for in vivo imaging of platelet-rich thrombus and endothelial activation. J Nucl Med 2011;52:1433–40.
28. Davey R, Bamford J, Emery P. The role of endothelial dysfunction in the pathogenesis of neuropsychiatric systemic lupus erythematosus. Lupus 2010;19:797–802.
29. Futrell N, Millikan C. Frequency, etiology, and prevention of stroke in patients with systemic lupus erythematosus. Stroke 1989;20:583–91.
30. Morelli S, Bernardo ML, Viganego F, et al. Left-sided heart valve abnormalities and risk of ischemic cerebrovascular accidents in patients with systemic lupus erythematosus. Lupus 2003;12:805–12.
31. Roldan CA, Gelgand EA, Qualls CR, Sibbitt WL. Valvular heart disease as a cause of cerebrovascular disease in patients with systemic lupus erythematosus. Am J Cardiol 2005;95:1441–7.
32. Roldan CA, Gelgand EA, Qualls CR, Sibbitt WL. Valvular heart disease is associated with non-focal neuropsychiatric systemic lupus erythematosus. J Clin Rheumatol 2006;12:3–10.
33. Roldan CA, Gelgand EA, Qualls CR, Sibbitt WL. Valvular heart disease by transthoracic echocardiography is associated with focal brain injury and central neuropsychiatric systemic lupus erythematosus. Cardiology 2007;108:331–7.
34. Moyssakis I, Tektonidou MG, Vasilliou VA, Samarkos M, Votteas V, Moutsopoulos HM. Libman-Sacks endocarditis in systemic lupus erythematosus: prevalence, associations, and evolution. Am J Med 2007;120:636–42.
35. Rademacher J, Sohngen D, Specker C, Janda I, Sitzer M. Cerebral microembolism, a disease marker for ischemic cerebrovascular events in the antiphospholipid syndrome of systemic lupus erythematosus? Acta Neurol Scand 1999;99:356–61.
36. Kumral E, Evyapan D, Keser G, et al. Detection of microemboli signals in patients with neuropsychiatric lupus erythematosus. Eur Neurol 2002;47: 131–5.
37. Dahl A, Omdal R, Waterloo K, et al. Detection of cerebral embolic signals in patients with systemic lupus erythematosus. J Neurol Neurosurg Psychiatry 2006;77:774–9.
38. Cantú-Brito C, Baizabal-Carvallo JF, Alonso-Juárez M, García-Ramos G. The clinical significance of microembolic signals in patients with systemic lupus erythematosus. Neurol Res 2010; 32:134–8.
39. Azarpazhooh MR, Mokhber N, Orouji E, et al. Microembolic signals in patients with systemic lupus erythematosus. Can J Neurol Sci 2010;37: 371–5.
40. Devinsky O, Petito CK, Alonso DR. Clinical and neuropathological findings in systemic lupus erythematosus: the role of vasculitis, heart emboli, and thrombotic thrombocytopenic purpura. Ann Neurol 1988;23:380–4.
41. Ellis SG, Verity MA. Central nervous system involvement in systemic lupus erythematosus: a review of neuropathologic findings in 57 cases, 1955–1977. Semin Arthritis Rheum 1979;8: 212–21.
42. Roldan CA, DeLong C, Qualls CR, Crawford MH. Characterization of valvular heart disease in rheumatoid arthritis by transesophageal echocardiography and clinical correlates. Am J Cardiol 2007;100:496–502.
43. Hanly JG, Fisk JD, McCurdy G, Fougere L, Douglas JA. Neuropsychiatric syndromes in patients with systemic lupus erythematosus and rheumatoid arthritis. J Rheumatol 2005;32:1459–66.
44. Turiel M, Muzzupappa S, Gottardi B, Crema C, Sarzi-Puttini P, Rossi E. Evaluation of cardiac abnormalities and embolic sources in primary antiphospholipid syndrome by transesophageal echocardiography. Lupus 2000;9:406–12.
45. Kiliç A, Unüvar E, Tatli B, et al. Neurologic and cardiac findings in children with Sydenham chorea. Pediatr Neurol 2007;36:159–64.
46. Cho BS, Kim HS, Oh SJ, et al. Comparison of the clinical manifestations, brain MRI and prognosis between neuroBechet's disease and neuropsychiatric lupus. Korean J Intern Med 2007;22:77–86.

Key Words: cerebrovascular disease ■ Libman-Sacks endocarditis ■ microembolism ■ stroke ■ transesophageal echocardiography.

APPENDIX

For supplementary figures, tables, and videos, please see the online version of this article.